Remarks

Oath/Declaration

The petition was previously submitted in parent application no. 09/867,693. The petition was granted on December 03, 2001. It is not apparent that it needs to be reviewed again and granted again.

Information Disclosure Statement

Applicants gratefully acknowledge the examiner-initialed two sheets of references which applicants submitted on September 8, 2003.

Amendments

The independent claims have been amended to recite that the rods have a diameter of 10-20 nm by transmission electron microscopy. This is supported in the specification in originally filed claims 6, 15, 41, 49, and 56. In addition, the independent claims have been amended to recite that the complexes are colloidally stable in normal saline. This is supported at page 22 lines 5-7 of the specification. Other amendments correct antecedent basis and cancel redundant claims and claim recitations in view of the amendments to the independent claims.

The specification has been amended to unify the references to the complexes denoted as Plasmin™. These are now referred to as DNA complexes which is supported at page 17, lines 6-7: "we have developed reagents and formulation methods that compact single molecules of plasmid DNA into 20-25 nm particles (PLASmin™ complexes)."

Rejection of Claims 1-19, 26-28, 30-31, 34-42, 51-82, 103-104, 106-109,114-117, and 122 Under 35 U.S.C. §112, First Paragraph

The claims are rejected for failing to adequately support and enable a composition comprising only rod-shaped complexes. This rejection is respectfully traversed.

The language of claims 1, 8, 17, 26, and 28 has been amended to clarify that the composition need not be homogeneous, *i.e.*, that all complexes in the composition need not be rod-shaped. Applicants thank the examiner for pointing out this inconsistency between the claim language (which seemed to require homogeneity) and the disclosure (which did not teach a homogeneous preparation). The claims as amended are consistent with the specification.

Applicants also take this opportunity to clarify an apparent misunderstanding of the specification. The Office Action states that the specification is drawn to complexes in the shape of a condensed sphere. Paper No. 20060726 at page 5, line 6. The condensed sphere which is often referred to is merely a hypothetical complex which is used to compare to the size of actual complexes. See *e.g.*, page 2, line 20. ("The complex is compacted to a diameter which is less than (a) double the theoretical diameter of a complex of said single nucleic acid molecule and a sufficient number of polycation molecules to provide a charge ratio of about 1:1, in the form of a condensed sphere...."). Such hypothetical complexes are not the actual complexes which are claimed herein.

It is respectfully submitted that the specification enables and supports the compositions as recited in the claims as amended.

The same claims are rejected because a 1995 report (Orkin) found gene therapy not ready for the clinic. Today, however, eleven years later, the situation has developed considerably. As noted, the present claims are directed to particles and their delivery to cells. Applicants submit herewith a paper published in 2004, Konstan et al., Human Gene Therapy, 15:1255-1269. Konstan shows that the complexes of the present invention, when administered to human subjects with Cystic Fibrosis, are able to reconstitute partial to complete Cystic Fibrosis Transmembrane Regulator (CFTR) function. The particles and how they were made are described at page 1258, column 1: "The acetate salt of $CK_{30}P10K$ biconjugate was mixed with plasmid DNA such that complexes were formed having essentially one positive charge for each negative charge on the DNA. The DNA was condensed into tightly compacted rod-shaped structures having a diameter

of about 12-15 nm and a length of about 100-300 nm." Konstan et al. report functional evidence of vector-derived CFTR chloride channel reconstitution. Thus, the particles of the present invention overcome problems noted in the cited prior art.

The Office Action points to an alleged "need for prolonged gene expression in a successful non-viral gene therapy." However, there is no need for prolonged expression when re-dosing is simple and feasible. Moreover, because the target cells have a finite life-span, re-dosing will be necessary to transfect newly formed cells after the originally transfected cells die. It is respectfully submitted that the present invention overcomes obstacles formerly encountered or imagined in the prior art as shown by Konstan et al., submitted herewith.

The Rejection of Claims 1-2, 8-9, 11-12, 17, 20, 26, 28, 38, and 102-104 Under 35 U.S.C. §102(b)

Wolff (US 6,126,964) is cited as teaching all of the limitations of each of the rejected claims. Applicants respectfully traverse.

First, the rejection asserts that Wolff teaches a counterion of acetate for the polycation. Paper No. 2006721, page 10, lines 7-9. However, Wolff teaches the combination of compound 6 with ethyl acetate and methanol and hydrochloric acid. The counterion of compound 6 is bromine (Br-), not acetate. After the reaction, compound 7 is formed. It, too, has bromine as a counterion – not acetate. There is also no indication that compound 6, a polycation, is combined with nucleic acid, as would be required in the claimed invention.

Second, contrary to the assertion of the Patent Office, Wolff's complexes are not rods. Rather, the small particles of Wolff are spheroids. See Fig. 2. The particles have diameters of 40-70 nm (column 5, lines 1-3) as distinct from the 10-20 nm of the present invention. See also column 14, lines 41-44.

Thus, Wolff fails to anticipate the claimed invention because it does not teach all claim elements.

The Rejection of Claims 1-2, 8-9, 11-12, 17-18, 26, 28, 30, 34, 36, 38, 53, 65, 78, 85, 92, and 102-103 Under 35 U.S.C. §102(b)

Hanson (US 5,844,107) is cited as anticipating the enumerated claims. This rejection is respectfully traversed.

Hanson's complexes are not rods of 10-20 nm diameter. Hanson describes his relaxed toroids of increased size as "rod-like." These relaxed toroids are "of increased size," *i.e.*, larger than the properly condensed toroids of <30 nm in diameter. See column 62, lines 51-54. Thus, even if Hanson's rod-like toroids were considered "rods," *arguendo*, they were not rods of 10-20 nm diameter as recited in the claims.

Thus, it is respectfully submitted that Hanson fails to teach all elements of the claims.

The Rejection of Claims 3, 10, 19, 31, 35, 37, 51-53, 63-65, 67-68, 76-78, and 104 Under 35 U.S.C. §103(a) over Hanson, Park, and Schacht

The Rejection of Claims 58-62, 66, 73-75, 79-82, and 122 Under 35 U.S.C. §103(a) over Hanson, Park, and Mao

The Rejection of Claims 4-7, 13-16, 39-42, 54-57, 69-72, 106-109, and 114-117 Under 35 U.S.C. §103(a) over Hanson, Park, Schacht, and Kwoh

Hanson is the primary reference in each of these rejections. Hanson has been discussed above, and its deficiencies in teaching the subject matter of the claims 1-2, 8-9, 11-12, 17-18, 26, 28, 30, 34, 36, 38, 53, 65, 78, 85, 92, and 102-103 are enumerated. Briefly, Hanson does not teach rods of 10-20 nm diameter as recited in the claims.

The secondary references are cited to supply a teaching of a recitation in a dependent claim. Park is cited to teach PEGylated polylysine. Schacht is cited to teach attachment of PEG to polylysine via a disulfide bond. Mao is cited to teach lyophilization and rehydration prior to

administration. None of these, however, cure the deficiency of Hanson which fails to teach rod-shaped complexes of 10-20 nm diameter formed using a polycation with an acetate counterion.

Kwoh, however, is cited as teaching rod-shaped complexes of diameter less than 25 nm. Even so, Kwoh does not teach remaining elements of the claims as amended. The claims have been amended to recite colloidal stability in normal saline. Kwoh's complexes do not share this property.

Kwoh teaches the instability of her complexes in a number of different ways. In Table 1, Kwoh compares the size of her polylysine complexes (PLL10K and PLL26K) in water to the size in 0.15 M NaCl. The complexes aggregate in the saline, increasing particle size by 5-fold. See also Fig.3A, where the complexes in NaCl have larger diameters at all charge ratios. Similarly, Kwoh teaches that PEG-lysine complexes are not colloidally stable in physiological saline. Complexes made with DNA and PLL10K-PEG5K have a diameter of 80.5 nm in water, which increases to 187 nm in saline (see page 185, column 1, lines 12 to column 2, line 3.)

Because the prior art does not teach or suggest all elements of the claimed methods and because there would have been no reasonable expectation of success in combining various teachings to achieve the present invention, the rejection should be withdrawn. All pending claims should thereafter be allowed.

Respectfully submitted,

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